Proposed Decision Memo for Serum Iron Studies (Addition of Restless Leg Syndrome as a Covered Indication) (CAG-00263R)

Decision Summary

CMS is seeking public comment on our proposed determination that there is insufficient evidence to add restless legs syndrome as a covered indication in the narrative of the Serum Iron Studies National Coverage Determination (NCD) at Section 190.18 of the NCD Manual. Local Medicare contractors may continue to provide coverage on a case by case basis based on additional documentation submitted by the provider with the claim.

We propose to issue a National Coverage Determination (NCD) that does not change the current Serum Iron Studies NCD. That is, restless legs syndrome would remain on the ICD-9-CM Codes that Do Not Support Medical Necessity list, and providers seeking coverage for the clinical laboratory diagnostic test would continue to submit additional documentation to support a determination of medical necessity.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG #00263R
Serum Iron Studies (Addition of Restless Leg Syndrome as a Covered Indication)

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SUBJECT: Proposed Decision Memorandum for Serum Iron Studies (Addition of Restless Leg Syndrome as a Covered Indication)

DATE: August 9, 2006

I. Proposed Decision

CMS is seeking public comment on our proposed determination that there is insufficient evidence to add restless legs syndrome as a covered indication in the narrative of the Serum Iron Studies National Coverage Determination (NCD) at Section 190.18 of the NCD Manual. Local Medicare contractors may continue to provide coverage on a case by case basis based on additional documentation submitted by the provider with the claim.

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We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

II. Background

We are providing detailed information about the diagnosis and treatment of restless leg(s) syndrome (RLS) below. Though the NCD being reconsidered refers to a diagnostic test, Serum Iron Studies, we believe the readers' grasp of the proposed decision can be enhanced by a broader discussion of the disease for which test coverage was requested.

RLS is a sensory-motor disorder that often has a profound impact on sleep. Though it was first described over 300 years ago (Willis, 1685), the term restless legs syndrome was coined by the Swedish neurologist Ekbom in 1945, and it was characterized by the "ill-defined" sensations of discomfort in the legs and feet requiring frequent leg movement (Ekbom, 1945). At the time he also noted that RLS most commonly occurred at night, and could cause severe insomnia. Based on modern research, RLS is felt to be a relatively common disorder that often occurs just before sleep, especially in persons 50 years and older. Symptoms of RLS are exacerbated by inactivity and temporarily relieved by movement. The severity of the symptoms varies widely, ranging from occurring only occasionally in a stressful situation to nightly and severe, with almost total disruption of sleep.

After the discovery of nocturnal myoclonus (Symonds, 1953) and the polysomnographic evaluation of subjects with RLS, (Lugaresi, Tassinari, Coccagna, Ambrosetto, 1965) RLS started to receive more clinical recognition. The diagnosis of RLS is based on clinical findings; criteria for identifying patients with the condition were established by the American Academy of Sleep Medicine and were included in the International Classification of Sleep Disorders (1990) as dyssomnia and intrinsic sleep disorders. The International Restless Legs Syndrome Study Group (IRLSSG) emphasizes four essential criteria together with additional clinical findings in making a diagnosis of RLS (Walters, IRLSSG, 1995; Allen, Piccietti, Hening, Trenkwalder, 2003):

1. the desire to move the limbs associated with paresthesia/dysesthesia;
2. motor restlessness and relief with movement;
3. worsening or exclusive presence of symptoms at rest (lying, sitting) with at least partial or temporary relief by activity, and
4. symptoms worsening during evening/night (circadian pattern).

Additional clinical features of RLS include:

1. sleep disturbance and its consequences;
2. involuntary movementsperiodic limb movement during sleep (PLMS), periodic limb movement during wakefulness (PLMW), and non-periodic limb movement (NPLM);
3. unremarkable neurological examinationno abnormalities in idiopathic or primary forms;
4. waxing and waning clinical course in mild forms or progressive in moderate to severe forms, and
5. positive family history in 40-50% of cases, with an autosomal dominant mode of inheritance.

Though 15% of affected individuals do not experience any sensory symptoms, the majority of patients report sensations in the legs ranging from creepy, crawling, or bubbling, to burning, tingling or pain, resulting in the desire to move. Symptoms can affect both lower extremities simultaneously, or can be unilateral or alternating in nature. In half of the cases, the arms are also involved (Montplaisir Boucher et al., 1997) and about one-fourth of all patients with RLS have symptoms on a daily basis (Allen, Hening, Montplaisir, Walters et al., 2002).

RLS is associated with two main features: poor sleep (reported in 95% of RLS subjects) and periodic limb movements during sleep (PLMS, reported in 80% of RLS patients). Initially, symptoms may be occasional, but become continuous and more severe with time. RLS is a major cause of sleep disturbance. Patients with RLS suffer from insomnia and disturbed sleep which can lead to daytime drowsiness and its consequences. Patient distress and sleep loss may be severe.

Epidemiology

RLS occurs in 1 to 5% of young to middle-aged adults, and increases to 10 to 20% in those 60 years and older (Harrison's Principles of Internal Medicine 16th edition, 2005). Based on these estimates, between 11 million and 31 million Americans suffer with this condition. RLS occurs twice as often in females as in males (Berger, Luedemann, Trenkwalder et al., 2004), and is most severe in middle-aged or elderly persons, in whom it has a chronic progressive course. RLS occurs more commonly in those with Northern European ancestry, and approximately one-third of patients (especially those with early-onset disease) will have multiple affected family members. Some researchers have also noted that early-onset RLS (starting before the age of 20) is more likely to occur in first-degree relatives than late onset RLS, and is more likely to be associated with idiopathic RLS (Allen, La Buda et al., 2002; Bassetti, Mauerhofer, Gugger et al., 2001). In some surveys from Asia, the prevalence is extremely low, suggesting a possible ethnic and racial difference in RLS prevalence. Phillip and associates performed a survey on almost 2000 subjects with RLS in the state of Kentucky, and found that in this group RLS was noted to be associated with subjects with increased age and body mass index, lower income, smokers, lack of exercise, low alcohol consumption, and diabetes (Phillips, Young, Finn et al., 2000). Banno and associates using the Providence of Manitoba Health database showed that RLS was much more likely to be documented in patients with extrapyramidal disorders, musculoskeletal problems, depression, as well as problems with joint and back disorders (Banno, Delaive Walld, Kryger, 2000). Rothdach and associates, while performing a population-based survey of Augsburg's elderly suffering with RLS, were also able to replicate the findings of increased depression in this group (Rothdach, Trenkwalder et al., 2000).

As noted in a review by Zucconi and associates, RLS has been classified as either idiopathic (primary, comprising 60 to 80% of all RLS) or secondary (symptomatic) in nature (Zucconi, Ferini-Strambi, 2004). According to Zucconi, the primary form of RLS might be defined as cryptogenic, indicating that in most instances the etiology and pathogenesis are unknown, leaving open the possibility of finding the exact origin and mechanism. Primary RLS has a familial component (40-60% of the cases). Some authors have suggested that iron deficiency and renal failure may be secondary causes of RLS (Harrison's Principles of Internal Medicine 16th edition, 2005) but the evidence is inconsistent in this regard. Other conditions associated with RLS include pregnancy, peripheral neuropathies, neuropathies and radiculopathies, syringomyelia, rheumatologic disorders, diabetes, Parkinson's disease and psychological/psychiatric disorders (extrapyramidal disorders). Severe forms of RLS that lead to the seeking of medical treatment probably represent around 15% of the total number of patients suffering with RLS.

Disease process

Though a number of theories have been proposed, no etiology has currently been found for RLS. Based on one theory, RLS is thought to result from a complex interaction between the central and peripheral nervous system. Bara-Jimenez and associates have noted that patients with RLS have enhanced spinal cord excitability compared to age-matched non-RLS patients, especially at night (Bara-Jimenez, Aksu, Graham, et al., 2000), but other reviews suggest sub-cortical dysfunction, and no evidence of primary cortical involvement in RLS activity (Allen, Earley, 2001).

A second theory suggests the cause of RLS may be related to disruption of the subcortical dopamine system. Numerous authors have reported that symptoms related to RLS respond to dopaminergic agonist, and is exacerbated by centrally-acting dopaminergic antagonist (Allen, Earley, 2001; Akpinar, 1987; Wetter, Stiasny, Winkelmann, 1999; Young, Piovesan, Biglan, 2003). Another theory suggests that RLS results from a deficiency of dopaminergic function based on abnormalities of iron transport and storage resulting in a neurodegenerative process (Earley, Allen, Beard, Connor, 2000; Krieger, Schroeder, 2001; Connor, Wang, Patton, Menzies et al., 2004; Connor, Boyer, Menzies, Allen et al., 2003).

As noted earlier a number of authors contend that iron deficiency (with and without anemia) is a secondary cause of RLS, and some authors have noted that ferritin levels seems to be associated with severity of RLS (Rich, 2000; O'Keeffe 2005; Clardy, Earley, Allen et al., 2006; Mizuno, Mihara, Miyaoka et al., 2005). Some authors have reported that iron supplementation seems to improve symptoms related to RLS (Earley, Heckler, Allen, 2004; Earley, Heckler, Allen, 2005; Sloand, Shelly, Feigin, Bernstein, Monk, 2004).

Diagnosis

Despite the relative high prevalence of RLS, it is often under reported by patients and misdiagnosed by physicians. In a large multi-national study done by Allen and associates which consisted of more than 23,000 subjects, less than half of the 2223 patients with RLS symptoms actually discussed the condition with their physician, and only about 7% were actually diagnosed with RLS (Allen, Hening, Montplaisir, Walters et al., 2002). In a large multi -national primary care population study, Hening and associates noted that 65% of RLS sufferers had reported consulting a physician about their symptoms, but only 25% were given a diagnosis (Hening, Walters, Allen, Montplaisir et al., 2004).

The diagnosis of RLS is made on history alone based on the IRLSSG criteria, emphasizing four essential characteristics along with additional clinical findings. Secondary causes of RLS may be ruled out by further evaluation. Generally a referral to a sleep specialist is not needed, although polysomnography (PSG) with bilateral anterior tibialis electromyography (EMG) monitoring to rule out other forms of sleep disturbance (e.g., obstructive sleep apnea, narcolepsy-cataplexy syndrome), as well as a Suggested Immobilization Test (SIT) to rule out periodic limb movements, can be used to support the diagnosis of RLS. PSGs are ordered due to difficulties in sleep onset, maintaining sleep during the night, and sleep fragmentation, as well as to detect the evidence of periodic legs movements during sleep and wake. Using neurophysiologic parameters, Akyol and associates were not able to demonstrate electrophysiological changes in persons suffering with RLS compared to controls (Akyol, Kiyliogu et al.., 2003).

The clinical diagnosis of RLS includes the following four sensory motor features:

- the urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations, primarily in the legs (generally below the knees) but sometimes in the arms;
- the urge to move or uncomfortable sensations that begin or worsen during rest and repose or inactivity;
- the urge to move or uncomfortable sensations that are partially or totally relieved by movement, at least in the beginning of the illness, and at least as long as the activity continues; and
- the uncomfortable sensations or the urge to move are worse in the evening or early part of the night than during the day.

Supportive diagnostic criteria include responsiveness to dopaminergic drugs, at least early in the disease.

There are a number of measurement tools used to gauge the severity of symptoms. Some commonly used validated instruments include the International Restless Legs Syndrome Rating Scale (IRLS Scale) (The International Restless Legs Syndrome Study Group, 2003; Walters, LeBrocq, Dhar, Hening, et al., 2003) the 10 item IRLS (Wunderlich Evans et al., 2005), the Clinical Global Impression-Global Improvement scale (CGI-I), the Restless Legs Syndrome Quality of Life Questionnaire (RLSQoL) (Abetz, Vallow, 2005; the Restless Legs Syndrome Quality of Life Instrument (RLS-QLI) (Atkinson, Allen, DuChane et al., 2004); and the Johns Hopkins Restless Legs Severity Scale (Allen, Earley, 2001).

RLS and associated medical conditions

As noted above, a number of medical conditions have been associated with RLS. Pregnancy was one of the first conditions found to be associated with RLS (Ekbom, 1960). This has been confirmed subsequently (Winkelmann, Wetter, Collado-Seidel, Gasser et al., 2000). A number of authors have noted an association between RLS, pregnancy and anemia (Zucconi Ferini-Strambi, 2004; Masood, Phillips, 2001; Berger, von Eckardstein, et al., 2002; Akyol, Kiylioglu et al., 2003). A number of studies relate RLS, pregnancy and iron deficiency anemia, but others have challenged this relationship. For instance, a number of researchers have hypothesized that RLS' association with pregnancy could likely be due to folate deficiency either alone or in conjunction with iron deficiency, at least during part of the pregnancy (Botez, 76; Manconi, De Vito, Economou et al., 2004). In a sample of pregnant women, Lee and associates were able to demonstrate that reduced serum folate, rather than indicators of iron deficiency anemia (serum ferritin, serum iron, and hemoglobin) or pernicious anemia (vitamin B_{12}), is associated with RLS (Lee, Zaffke, Baratte- Beebe, 2001). The relationships between RLS and both forms of anemia are tenuous.

Neuropathies and radiculopathies associated with RLS have been noted in different groups, including those with uremia, polyneuropathy, and amyloidosis (Callaghan, 1966; Rutkove, Matheson et al., 1996; Salvi, Montagna, Plamati et al., 1990). In a study performed by Ondo and Jankovic, clinical as well as EMG confirmation of neuropathy were found in 32% of a series of 54 consecutive patients with RLS (Ondo, Jankovic, 1996). Salih and associates also reported that RLS was associated with up to 25% of cases of rheumatoid arthritis compared to 4% of controls with osteoarthritis or seronegative arthropathies, and was associated with greater disease activity and severity (Salih, Gray, Mills et al., 1994). In another laboratory study, 68 patients with RLS failed to show an association with rheumatologic serologies (Ondo, Tan, Mansoor, 2000). Other rheumatologic conditions reported to be associated with RLS include Sjogren's syndrome (Gudbjornsson, Broman et al., 1993) and fibromyalgia. (Yunus, Aldag, 1996).

Varicose veins have also been associated with RLS, and treatment of varicose veins and chronic venous insufficiency has been reported to be effective for this condition. In one study, Kanter noted that 312 of 1,397 subjects seeking treatment for varicose veins had symptoms of RLS found on screening questionnaire and interviews. Sclerotherapy was performed in 113 of the patients with RLS; 98% reported initial relief of RLS, and symptom relief was maintained in 72% at 2-year follow-up (Kanter, 1995). Studying the use of hydroxyethylrutoside (HR) in patients with RLS, Poynard and associates performed a meta-analysis of 15 trials including 1,973 patients with RLS. The study revealed that 36% of those treated with HR noted improvement of symptoms compared to the 26% in the control group (Poynard, Valterio, 1994).

Diabetes has often been reported to be associated with RLS. However, a large clinical study performed by Banno and associates failed to demonstrate a high prevalence of diabetes in patients with RLS (Banno, Delaive, Walld, Kryger, 2000). Winkelman and associates found that 20-25% of patients with end-stage renal disease (ESRD) had overt signs of RLS (Winkelman, Chertow, Lazarus, 1996), while others noted up to 62% of patients with ESRD had RLS, but had a milder form of this condition (Hui, Wong, Ko et al., 2000). No correlation with iron levels or other uremic characteristics had been found in this study. O'Keeffe studied a group of 80 consecutive elderly patients with RLS (mean age = 71) and found that clinical neuropathy and iron deficiency was a common finding in this group (O'Keeffe, 2005).

Treatment Options

Non-pharmacologic treatment is temporary and of marginal benefit. Hot baths, muscle stretching, massages or moderate exercise may be of some help. Improved sleep hygiene and patient education improve patient outcomes. Pharmacologic treatment has demonstrated mixed results. Folate, elemental iron along with vitamin C, and vitamin B_{12} have been recommended, though improvement is inconsistent. Dopamine agonists as well as Levo-dopa are used first line for the primary form of RLS. Dopamine agonist agents (e.g., pramipexole or ropinirole) can provide symptom relief in up to 90% of patients with RLS, and can reduce symptoms related to PLMS by as much as 70 to 100% (Early, 2003; Thorpy, 2005). Second line treatments for RLS include narcotics, benzodiazepines, and certain anticonvulsants.

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage and not otherwise be excluded from coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services).

The current NCD (found in the National Coverage Determination Manual, CMS Pub. 100-03, section 190.18), effective November 25, 2002, indicates that the benefit category is "diagnostic laboratory tests." The information provided supports continuing the current benefit category of Social Security Act section 1861(s)(3), "diagnostic laboratory tests," for the new indication. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

In accordance with section 4554 of the Balanced Budget Act of 1997, CMS entered into negotiations with the laboratory community regarding coverage and administrative policies for clinical diagnostic laboratory services. As part of these negotiations, we promulgated a rule that included 23 NCDs, including Serum Iron Studies. The rule was proposed in the March 10, 2000, edition of the Federal Register (65 FR 13082) and was made final on November 23, 2001 (66 FR 58788). The final rule called for a 12-month delay in effectuating the NCDs in accordance with the recommendations of the negotiating committee. Thus, the NCDs became effective on November 25, 2002.

In the laboratory NCDs, CMS determined that specific tests were reasonable and necessary for certain medical indications. These decisions were evidence-based, relying on scientific literature reviewed by the negotiating committee. The NCDs contain a narrative describing the indications for which the test is reasonable and necessary. We also developed a list of ICD-9-CM codes that designate diagnoses/conditions that fit within the narrative description of indications that support the medical necessity of the test. This list is entitled “ICD-9-CM Codes Covered by Medicare,” and includes codes where there is a presumption of medical necessity.

In addition, we developed two other ICD-9-CM code lists. The second list is entitled “ICD-9-CM Codes Denied,” and lists diagnosis codes that are never covered by Medicare. The third list is entitled “ICD-9-CM Codes that Do Not Support Medical Necessity,” and includes codes that generally are not considered to support a decision that the test is reasonable and necessary, but for which there are limited exceptions. Tests in this third category may be covered when they are accompanied by additional documentation that supports a determination of reasonable and necessary.

Currently, RLS does not have a unique ICD-9-CM code. It is coded as 333.99 (Other), under 333.9 (Other and unspecified extrapyramidal diseases and abnormal movement disorders). This code does not appear in the list “ICD-9-CM Codes Covered by Medicare” or the list “ICD -9-CM Codes Denied” in the Serum Iron Studies NCD. Therefore RLS is included in the list “ICD-9-CM Codes that Do Not Support Medical Necessity” and Medicare contractors may provide coverage when the claim is accompanied by additional documentation that supports a determination of reasonable and necessary. *(Note: We have been informed that a specific ICD-9-CM code for RLS, 333.94, will go into effect October 1, 2006.)*

Since the NCD narrative does not currently contain language that would allow RLS to be added to the list “ICD-9-CM Codes Covered by Medicare,” we are evaluating the request to add RLS as an indication to the NCD narrative itself, which, if approved, would be followed by the code addition.

The current NCD lists the following indications and limitations:

Indications
1. Ferritin, iron and either iron binding capacity or transferrin are useful in the differential diagnosis or iron deficiency, anemia and for iron overload conditions.
a. The following presentations are examples that may support the use of these studies for elevating iron deficiency: Certain abnormal blood count values (i.e., decreased mean corpuscular volume (MCV), decreased hemoglobin/hematocrit when the MCV is low or normal, or increased red cell distribution with width (RDW) and low or normal MCV); abnormal appetite (pica); acute or chronic gastrointestinal blood loss; hematuria; menorrhagia; malabsorption; status post-gastrectomy; status port-gastrojejunostomy; malnutrition; preoperative autologous blood collection(s); malignant, chronic inflammatory and infectious conditions associated with anemia which may present in a similar manner to iron deficiency anemia; following a significant surgical procedure where blood loss had occurred and had not been repaired with adequate iron replacement.
b. The following presentations are example that may support the se of these studies for evaluating iron overload: chronic hepatitis; diabetes; hyperpigmentation of skin; arthropathy; cirrhosis; hypogonadism; hypopituitarism; impaired porphyrin metabolism; heart failure; multiple transfusions; sideroblastic anemia; thalassemia major; cardiomyopathy, cardiac dysrhythmias and conduction disturbances.
2. Follow-up testing may be appropriate to monitor response to therapy, e.g., oral or parenteral iron, ascorbic acid, and erythropoietin.
3. Iron studies may be appropriate in patients after treatment for other nutritional deficiency anemia, such as folate and vitamin B12, because iron deficiency may not be revealed until such a nutritional deficiency is treated.
4. Serum ferritin may be appropriate for monitoring iron status in patients with chronic renal disease with or without dialysis.
5. Serum iron may also be indicated for evaluation of toxic effects of iron and other metals (e.g., nickel, cadmium, aluminum, lead) whether due to accidental, intentional exposure or metabolic causes.

Limitations

1. Iron studies should be used to diagnose and manage iron deficiency or ion overload states. These tests are not to be used solely to assess acute phase reactants where disease management will be unchanged. For example, infections and malignancies are associated with elevations in acute phase reactants such as ferritin, and decreases in serum iron concentration, but iron studies would only be medically necessary if results or iron studies might alter the management of the primary diagnosis or might warrant direct treatment of an iron disorder or condition.
2. If a normal serum ferritin level is documented, repeat testing would not ordinarily be medically necessary unless there is a change in the patient's condition, and ferritin assessment is needed for the ongoing management of the patient. For example, a patient presents with new onset insulin-dependent diabetes mellitus and has a serum ferritin level performed for the suspicion of hemochromatosis. If the ferritin level is normal, the repeat ferritin for diabetes mellitus would not be medically necessary.
3. When an End Stage Renal Disease (ESRD) patient is tested for ferritin, testing more frequently than every three months requires documentation of medical necessity (e.g., other than chronic renal failure or renal failure, unspecified).
4. It is ordinarily not necessary to measure both transferring and TIBC at the same time because TIBC is an indirect measure of transferrin. When transferrin is ordered as part of the nutritional assessment for evaluating malnutrition, it is not necessary to order other iron studies unless iron deficiency or iron overload is suspected as well.
5. It is not ordinarily necessary to measure both iron/TIBC (or transferrin) and ferritin in initial patient testing. If clinically indicated after evaluation of the initial iron studies, it may be appropriate to perform additional iron studies either on the initial specimen of on a subsequently obtained specimen. After a diagnosis of iron deficiency or iron overload is established, either iron/TIBC (or transferring) or ferritin may be medically necessary for monitoring, but not both.
6. It would not ordinarily be considered medically necessary to do a ferritin as a preoperative test except in the presence of anemia or recent autologous blood collections prior to the surgery.

IV. Timeline of Recent Activities

February 28, 2006	CMS opened a reconsideration of the Serum Iron Studies national coverage determination (NCD) for review of adding restless leg syndrome to the covered indications in response to receipt of a formal request from Karen H. Rice, M.D., Capital City Medical Associates, Jefferson City, Missouri. The initial 30 day public comment period began.
March 30, 2006	End of public comment period.

V. FDA Status

The FDA has approved many tests of serum iron status. These can be found on the FDA website at URL http://www.fda.gov/cdrh/oivd/index.html.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

A detailed account of the methodological principles of study design that agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

We are providing a summary of the evidence we considered during our review. We will, of course, consider additional evidence submitted through the public comment period. The evidence reviewed to date in this proposed decision memorandum includes the published medical literature on pertinent clinical studies of serum iron and RLS.

A reasonable and necessary diagnostic test must provide information that is used by the treating physician to appropriately guide the management of the patient's specific medical problem. A principal outcome of interest in assessing the utility of a diagnostic test for this purpose is its ability to improve health outcomes of persons who are tested. It can be difficult to conclusively prove that changes in ultimate outcomes such as mortality are the result of a diagnostic test. Some disease courses are not significantly altered by the timing of treatment. If therapeutic options are few, the patient may receive the same treatment regimen upon diagnosis regardless of subsequent test results.

Intermediate outcomes may in some cases form an adequate basis from which to draw conclusions of benefit for a diagnostic test. This is predicated on the characteristics of the specific disease in question and the characteristics of potential treatments for that disease. Improved intermediate outcomes from tests might include earlier treatment when early treatment improves survival or quality of life, the avoidance of unnecessary and possibly harmful treatment, the choice of a more appropriate patient-targeted treatment, and for life-threatening diseases, the prognostic information needed for timely referral to support systems such as hospice.

In general, the published medical literature on diagnostic testing focuses on measures of test accuracy rather than directly reporting on the ultimate or even intermediate patient health outcomes that result from physician action based on a particular test result. To determine if a diagnostic test is beneficial, we may review a chain of evidence, examining the links from initial suspicion of disease to actual diagnosis and then to choice of treatment and then to health outcomes.

B. Discussion of evidence reviewed

1. Question

Is the quality of evidence adequate to conclude that the results of serum testing for iron, ferritin, iron binding capacity and/or transferrin, when used by the treating physician to guide management of the patient's medical problem, improve health outcomes in persons with restless leg syndrome?

The available published medical literature does not allow us to address this question directly. So to address this central question, CMS considered the potential ways in which serum iron testing might be relevant to RLS, and thus also considered two subsidiary questions.

- Is there adequate evidence that accepted diagnostic criteria require serum iron testing results for the diagnosis of RLS?
- Is there adequate evidence that iron supplementation, which would then be accompanied by serum iron studies testing to monitor the treatment, is necessary to treat RLS?

Thus, to address the central question we believe it is appropriate in this instance to also search for evidence on the subsidiary questions as well.

2. External technology assessments

We did not request an external technology assessment on this issue and are unaware of any assessments that were conducted independently.

3. Internal technology assessments

Literature search methods

Medical literature was identified using MEDLINE, Cochrane Review, ECRI, as well as multiple oncology, surgery, and gynecology textbooks. Peer-reviewed articles written in English were reviewed. Search terms included restless legs syndrome; restless legs syndrome and iron deficiency anemia; restless legs syndrome and ferritin; restless legs syndrome and iron metabolism; restless legs syndrome and iron studies. We focused the review on original reports of the use of iron studies in the diagnosis and treatment of RLS in non-pregnant adults. We also reviewed original reports of the use of supplemental iron as a treatment for RLS, and other relevant articles.

Evidence Review

Nordlander, (1953): The author notes that in 1951 he observed 3 cases of anemia where restless legs developed in parallel to the anemia and resolved when the anemia was cured by blood transfusions. He subsequently used intravenous or oral iron therapy in other patients with iron deficiency anemia and restless legs, reporting symptom relief in 10 patients. He then administered intravenous iron to patients with restless legs without anemia and with normal serum iron, noting “[t]he effect was just as quick and complete as in the anemic patients…”

Ekbom, (1960): The author reviewed RLS, reporting a 24% incidence of RLS in patients with iron deficiency (< 60µg/dL). He noted personal experience with treating 10 iron deficient patients with iron injections, noting "…the results were highly satisfactory in every case." He described his experience with iron therapy in patients with normal serum iron as limited.

Telstad, Sørensen, Larsen et al., (1984): This is a multicenter, randomized, double-blind, placebo-controlled trial of carbamazepine for RLS, lasting 5 weeks. There were 181 enrolled subjects, of which 7 dropped out. Eighty-four received carbamazepine, and 90 received the placebo. Hemoglobin and iron levels were obtained, and the severity of symptoms was assessed using a 15 cm visual analog scale. One hundred seventy-four patients (122 women) were analyzed. Both carbamazepine and placebo groups showed a significant therapeutic effect ($p < 0.01$), though carbamazepine was more effective than placebo ($p < 0.03$).

Initially, 42 patients in the placebo group reported 7 attacks/wk. By week 3 and week 5, this figure had dropped to 23 and 19 respectively. Initially all subjects had at least one attack/wk. By week 3, 22 placebo patients reported 0 attacks/wk. By week 5, 24 placebo patients reported 0 attacks/wk. Serum iron results were not reported. The authors state that the blood sampling procedure was not adequately standardized.

O'Keeffe, Noel, Lavan, (1993): The authors assessed 420 consecutive patients presenting to an acute care medical service. After excluding 97 patients with cognitive impairment, and 16 for taking neuroleptic medications, 15/307 had RLS (11 women), 13/15 had insomnia and 10/15 reported "troublesome or frequent leg symptoms." The criteria for determining cognitive impairment were not reported; the diagnostic criteria for diagnosing RLS were bilateral nocturnal leg discomfort 1) including the calf or shin, 2) sensation accompanied by urge to move the legs and relieved by moving the legs, 3) symptoms were not of tingling, pins-and-needles, numbness, cramps, or burning sensations alone. Serum ferritin levels were obtained, with iron deficiency defined as a result below 18 µg/l. Among those with current insomnia, iron deficiency was present in 4/13 RLS patients and 8/134 controls. It is not explained why iron deficiency was not assessed in 2 (15-13 = 2) patients with RLS. The 4 patients with RLS and iron deficiency were started on ferrous sulfate three times daily. One died before follow-up. The remaining 3 reported substantial improvement. One patient with vitamin B_{12} deficiency had completely resolved symptoms within 1 month of treatment with vitamin B_{12}.

O'Keeffe, Gavin, Lavan, (1994): Eighteen elderly patients with RLS and 18 matched controls (median age 81), recruited from the wards and outpatient clinics of an acute-care geriatric unit, were rated for RLS severity on a 3-item questionnaire (0-10 point scale, 10 most severe) and these results were compared to serum ferritin levels. Subjects on iron supplementation were excluded. The criteria used to diagnose RLS are not described. The median ferritin was 33 µg/l in the RLS patients and 59 µg/l in the controls ($p < 0.01$). Patients with ferritin levels $\leq$ 45 µg/l were prescribed iron supplements as ferrous sulfate three times daily. Patients with ferritin levels between 46 and 100 µg/l were "…informed that their blood tests showed the possibility of a mild iron deficiency and a course of iron supplements might be beneficial. If they agreed, they were also started on iron supplements." It appears that all 5 of these patients were prescribed iron; one was unable to tolerate and another one died before follow-up. In total, 15 patients with RLS were prescribed iron and were available for follow-up analysis.

RLS severity and blood tests were repeated after 2 months of iron supplementation. All patients had higher ferritin levels (median increase 34 µg/l) and median RLS severity on the 10 point scale improved from 5 to 3. Two patients in the control group were reported to have ferritin levels below 18 µg/l.

Aul, Davis, Rodnitzky, (1998): Medical records of patients diagnosed with RLS at the University of Iowa Hospitals and Clinics from 1984 through 1996 were included in the study. Inclusion criteria were established, and according to the author, laboratory studies such as complete blood count (CBC), serum iron level, iron saturation and serum ferritin were included in the analysis. The study included 113 subjects, 72 (64%) were female and 41 (36%) were males. Subjects ages ranged from 24 to 90 years (mean age 64 +/- 14 years). Anemia as well as abnormal iron status was predefined in the study. Of the 80 patients that had a CBC, 17 (21%) were anemic. Of the 48 patients that had iron studies, 30 (62.5%) had low serum iron levels, and 37 subjects (77%) had low iron saturation. Of the 20 subjects that got ferritin levels, 5 (25%) were low. Of the 47 subjects that got both a CBC as well as iron studies, serum iron was low in 30 patients (63%), and in this group of 30 subjects only 10 (33%) were anemic. Iron saturation was low in 37 subjects (78%; 37 out of 47 subjects who got both CBCs and iron studies). Of these 37 subjects only 10 (27%) had anemia.

Collado-Seidel, Kohnen, Samtleben, et al., (1998): The authors interviewed 136 stable chronic hemodialysis patients treated in two centers in Germany, using the IRLSSG criteria to diagnose RLS. Each patient was classified into on of four groups: 1) Definitive RLS, 2) Questionable RLS, 3) RLS by history, or 4) Non-RLS. Thirty-two patients were in group 1, 88 in group 4. Laboratory studies, including serum ferritin, transferrin, and iron were obtained, and the authors compared the results for group 1 and group 4. Only intact parathyroid hormone (iPTH) showed a statistically significant difference between groups.

Sun, Chen, Ho et al., (1998): This is a retrospective review going back 4 years, including a total of 27 patients with RLS who had ferritin levels obtained at about the same time as a PSG. These 27 patients represent 26% of all the RLS patients presenting for initial RLS treatment during this time period. The authors report that 26 RLS patients were excluded because they did not have PSGs due to insurance limits, 1 patient was excluded for failure to complete the PSG, and the remainder for lack of timely ferritin testing. Patients were also excluded who had been on iron supplementation within 2 months of the PSG or on medications that might significantly alter PSG results. Ferritin levels are reported to correlate significantly with RLS severity ($r=0.43$, $p=0.02$). One subject in the highest severity group had the highest ferritin level (between 225 -250 mcg/l) of all. One subject in the lowest severity group had a ferritin level below 25 mcg/l. Sleep efficiency was positively correlated with ferritin level ($r=0.48$, $p=0.01$) but there was no significant relationship of ferritin level to PLMS/hr. The authors note in the discussion “While these results strongly support a relationship between ferritin and the severity of symptoms for patients with RLS, they do not in any way indicate that ferritin provides a screening test for RLS…Even among patients with RLS where the ferritin is related to severity, the relationship is far too variable to permit ferritin to be used as an assessment of the severity of RLS.”

Chesson, Wise, Davilla, et al., (1999): This report, entitled “Practice Parameters for the Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder,” was developed by the Standards of Practice Committee and approved by the Board of Directors of the American Academy of Sleep Medicine (AASM). Recommendation B.7. states, “Iron supplementation is effective in the treatment of RLS in patients with iron deficiency. [4.2.6.2;5.2] [Option] This recommendation is based upon level III to V evidence. Iron therapy may be more effective for patients with lower iron stores, but data are limited.”

Allen, Earley, (2000): Records for 26 consecutive RLS patients were analyzed for the effect of current age and serum ferritin on RLS severity for early- and late-onset (over 45) RLS. Fourteen early-onset and 12 late-onset subjects were included based on the IRLSG criteria. The JHRLSS was used to rate RLS severity. Polysomnogram (PSG) measurements including PLMS and serum ferritin levels were available. Data from subject reported in a previous study (Sun, Chen, Ho et al., 1998) were also included. The mean (± SD) serum ferritin (µg/l) was reported as 60.4 ± 65.2 in the early-onset group and 27.34 ± 27.8 in the late-onset group. The authors report that serum ferritin levels of early onset RLS patients showed no significant correlation with the JHRLSS or sleep efficiency. They did report a correlation between serum ferritin and JHRLSS and sleep efficiency in the late-onset group.

Davis, Rajput, Rajput, Aul, Eichhorn, (2000): The authors used medical records to identify 125 patients with RLS in their neurology clinic. Thirty-six respondents were screened and 28 patients were randomized to receive ferrous sulfate twice daily or placebo for 12 weeks. Anemia, defined as hemoglobin below 10, and current or recent iron therapy were among the causes for exclusion. Demographic data and iron studies were collected, and symptom severity was assessed. Twenty-four of the 28 patients met IRLSG criteria for RLS. The authors note that exclusion of the 4 other subjects does not change the results. Six of 14 patients withdrew from the iron group, 1/14 from the placebo group. No significant differences were noted in primary or secondary outcomes between the groups.

Earley, Connor, Beard, et al., (2000): CSF and serum were obtained from 16 patients with idiopathic RLS and 8 age-matched controls. Inclusion criteria included PLMS/hr > 15, a 1-year history of daily RLS symptoms, and a positive clinical response to levodopa. The mean CSF ferritin level was 1.11 ± 0.25 ng/mL in the RLS group compared to 3.50 ± 0.55 ng/mL in the control group ($p = 0.0002$). Mean CSF transferrin levels were 26.4 ± 5.1 mg/L in the RLS group compared to 6.71 ± 1.6 mg/L in the control group ($p = 0.018$). The authors conclude that the results indicate low brain iron in patients with RLS.

Allen, Barker, Wehrl, et al., (2001): The authors used MRI to measure brain iron in 5 subjects with RLS and 5 controls. Blinded reviewers assessed the images and rated RLS severity using the JHRLSS. They report decreases in iron concentration in the substantia nigra and putamen, and that the decreases were most clearly evident for patients with severe RLS.

Allen, Earley, (2001): This is a review of clinical and pathophysiologic features of RLS and does not report original research. The authors describe a model for RLS that postulates that brain iron deficiency leads to CNS dopamine abnormalities which in turn lead to RLS. They also note, “RLS is a clinical diagnosis that relies entirely on the patient’s symptoms…”

Berger, von Eckardstein, Trenkwalder, Rothdach, et al., (2002): This was a cross-sectional study examining the association between 5 measures of iron metabolism and RLS in the elderly population. Subjects, aged between 65 to 83 (n = 365), were examined neurologically and interviewed using the using standardized questions addressing the four criteria developed by the International Restless Leg Syndrome Study Group. Iron, ferritin, transferrin, soluble transferrin receptor, and C-reactive protein were analyzed. There were 36 patients identified with RLS. Though the study found that odds ratios of RLS were increased for iron and transferrin saturation in the fourth quintile (OR 3.08, 95% CI 1.02-9.29 and OR 5.68, 95% CI 1.18-27.26 respectively) compared to the middle quintile, there were no association with ferritin and soluble transferrin receptors. The authors also noted borderline significance for iron and transferrin saturation in the first (lowest) quintile. The authors concluded that there was no evidence to support that iron or ferritin deficiency were major causes of RLS in this population.

Ondo, Dat Vuong, Jankovic, (2002): This is one of the articles presented in the Garcia-Borreguero review below. The authors surveyed 320 consecutive clinic patients with PD (Parkinson’s disease), asking about the presence of RLS symptoms, using the Epworth Sleepiness Scale and other demographic and sleep measures. Seventeen patients were subsequently excluded for various reasons, leaving 303 for study. Sixty-three (20.8%) had RLS symptoms. Three to ten months after completion of the survey, ferritin levels were obtained from patients who were subsequently seen by one of the investigators, and the patients were again asked about the presence of RLS symptoms, and a stepwise regression was performed. The authors then added data from 46 additional PD/RLS patients, noting that the additional patients “were not necessarily collected systematically.” They then compared the 109 total patients with PD and RLS to 146 patients with only RLS from their database. They reported that lower serum ferritin levels were associated with RLS in their patients with PD.

Connor, Boyer, Menzies, et al., (2003): Using a post-mortem study design, seven brains of subjects suffering with RLS were compared with 5 age-matched subjects with no history of RLS. Iron studies, as well as immunohistochemical analysis (e.g., H and L-ferritin analysis) were performed to determine if any differences in iron metabolism existed between both groups. Although no histopathologic abnormalities were noted between the groups, iron staining as well as H-ferritin staining was decreased in the substantia nigra of RLS subjects. Also, though H-ferritin levels were difficult to detect in the substantia nigra of RLS subjects, L-ferritin staining was strong.

Garcia-Borreguero, Odin, Serrano, (2003): In this clinical review the authors discuss the possibility of a dopaminergic mechanism for RLS and an association with Parkinson's disease (PD). Their estimate of the prevalence of RLS in PD was derived from seven studies dating from 1960 to 2003. They note that three studies (total subjects = 400) found a similar prevalence to the general population, and that four studies (total subjects = 676) found a higher prevalence than the general population. Two of the four studies noted an association with low serum ferritin. They note that the evidence is limited and that large controlled studies are needed.

They report that in the original cohort of 303 patients, the mean (± SD) ferritin level (ng/mL) was 88.4 ± 67.5 for 32 of the 240 patients with PD without RLS, and 50.7 ± 46.6 for 25 of the 63 patients with PD and RLS. Of the total cohort, the mean ferritin level was 58.8 ± 51.0 for 46 of the 109 patients with PD and RLS, and 86.3 ± 63.0 for 90 of the 146 patients with RLS only.

Silber, Richardson, (2003): Consecutive patients with RLS during an 11-month period were asked whether they donated blood. All patients meeting the IRLSSG criteria for RLS who had donated blood at least 3 times per year for the preceding 3 years and had a serum ferritin below 20 µg/l were included. Of 245 patients with RLS, 8 met the inclusion criteria. All patients were instructed to cease blood donation, 2 were treated with oral iron alone, and 6 were treated with a combination of oral iron and RLS medication. RLS symptoms resolved in 3 patients and improved markedly in 5.

Connor, Wang, Patton, et al., (2004): Using cadaver specimens, the study consisted of 8 subjects; half were patients reported to have had RLS, the other half were controls. Neuromelanin cells taken from the substantia nigra were examined for iron management protein expression using immunoblot analysis. The results of the study revealed that ferritin, divalent metal transporter 1, ferroportin and transferrin receptor were decreased, and transferrin levels were increased in RLS subjects compared to controls. And though the total iron regulatory protein (IRP1 and IRP2) activity was decreased in RLS, total IRP2 protein levels were not decreased.

Earley, Heckler, Allen, (2004): Earley and associates administered 1000 mg of intravenous iron dextran in patients with RLS and reported that seven of ten subjects noted improvement in mean global RLS symptom severity, total sleep time as well as less hours with RLS symptoms and periodic leg movement, and that six of those ten could be classified as Responders at 2 weeks. Brain iron concentrations determined by MRI were reportedly increased in the substantia nigra and prefrontal cortex. They note "…the efficacy and safety of IV iron treatment for RLS remain to be established in double-blind studies."

Mizuno, Mihara, Miyaoka, et al., (2004): The study enrolled 10 non-treated subjects with RLS (IRLSG diagnostic criteria were used) and 10 age-matched control patients. Baseline demographics were similar. PSGs, electroencephalograms (EEGs), EMGs, as well as sleep stage scores were noted. Lumbar puncture and venous studies were recorded, as well as PLM index (measures leg movement) and PSQI-J global scores (measures subjective quality of sleep). Sleep latency was longer and the sleep efficiency was lower in the RLS group than in the non-RLS group. The PLM index was higher in the RLS group compared to the non-RLS group. No significant differences were seen in the PSQI-J global scores between both groups. No significant difference between serum iron, ferritin or transferrin levels were found between both groups, but CSF iron and ferritin levels were lower and transferrin levels were higher in patients with RLS compared to non-RLS subjects.

Silber, Ehrenberg , Allen, Buchfuhrer et al., (2004): This is described as a clinical review for clinicians rather than an evidence-based review, and does not present original data. The authors note in a comment that RLS may not be the only clinical indication of iron deficiency, and that clinicians should consider determining the serum ferritin level in all patients with RLS, especially those with conditions predisposing to blood loss.

Sloand, Shelly, Feigin, et al., (2004): Using a double-blind, placebo-controlled protocol, the investigators randomized 25 ESRD patients (11 treatment, 14 placebo) meeting IRLSSG criteria for RLS to 1000 mg of intravenous iron dextran or placebo. Blood chemistries as well as hematologic studies were obtained (including ferritin levels) at baseline. Demographic characteristics were similar between both groups. Serial studies were obtained weekly. The authors developed a 10-point severity scale (10 = worst). Following the participants through week four, the authors reported that patients receiving the iron supplement demonstrated improvement in RLS symptoms, but the improvement was noted to be greatest at week 2. The improvement of symptoms was associated with an increase in both serum and ferritin levels.

Earley, Connor, Beard, Clardy, Allen, (2005): The study consisted of 30 subjects (15 early-onset and 15 late-onset patients) along with 22 age-and-sex matched controls. The authors determined if: (1) patients with RLS and controls differed in regard to levels of ferritin and transferrin in the CSF, (2) patients with early-onset and late-onset RLS showed different outcomes for CSF values, and (3) CSF ferritin level correlated with disease severity. CSF and plasma specimens were obtained, and severity of illness was measured using the Johns Hopkins Restless Legs Severity Scale. The study revealed that nighttime CSF ferritin levels were lower in all RLS subjects compared to controls, and of the RLS subject, those with early onset (less than 45 years of age) had significantly lower ferritin levels than late onset or non-RLS subjects. The correlation between age of onset and CSF ferritin level had a value of r=0.64, indicating that the lower the age of symptom onset, the lower the CSF ferritin level. The study also noted that gender, as well as RLS subtype (early vs. late onset) has significant effect on ferritin levels. Also noted in the study, serum iron, TIBC, ferritin, transferrin, and serum ferritin receptor were not significantly different between RLS and control groups.

Earley, Heckler, Allen, (2005): Ten RLS subjects enrolled in a prior study in which they had received an intravenous infusion of 1000 mg of iron dextran were studied further. Those who had an initial response to the iron were asked monthly to give blood for ferritin determination and rate their symptom severity on a 10-point global rating scale (0 = very severe, 10 = no symptoms). Patients whose symptoms returned within two years of the initial infusion could receive additional iron supplementation if their ferritin was below 300 mcg/l and they were compliant with monthly follow-up and had remained off other RLS medications. Six of the original ten reported complete symptom relief, one of the six remained without symptoms. The 5 remaining were eligible for additional iron supplementation, but 2/5 were unable to complete the study. Slower rates of decline of ferritin were associated with more prolonged improvements.

Hogl, Kiechl, Willeit et al., (2005): This was a cross-sectional study of 701 randomly selected subjects, ages 50 – 89 years, from the general population of an Alpine region of northern Italy. RLS diagnosis was established based on IRLSSG criteria and severity was graded. The authors reported overall a 10.6% prevalence of RLS, 14.2% in women, 6.6% in men. Free serum iron, transferrin, and ferritin were similar in subjects with and without RLS, but soluble transferrin receptor concentrations were statistically significantly higher in subjects with RLS.

O'Keeffe, (2005): O'Keeffe also studied secondary causes of restless legs syndrome. Using 80 consecutive patients with RLS as subjects, he was able to show that iron deficiency (serum ferritin levels <50 ng/ml) was present in 22% of subjects with onset before age 50, 39% of those with onset at 50 to 64 years, and 58% of those with onset after 64 years (p=0.009).

O'Keeffe, (2005): The case report involved an 83-year-old male with a 2-year history of severe RLS (as documented by a high score on the IRLSSG scale). Though the subject had severe symptoms related to RLS and his bone marrow aspiration revealed iron stores were absent, his ferritin level was normal (93 mcg/L).

Siddiqui, Kavanagh, Traynor et al., (2005): This cross-sectional study included 127 dialysis patients who were diagnosed with RLS using the IRLSSG criteria, from a pool of 277 total patients. A number of variables were included in the study including the following: age, gender, medication profile, duration of renal replacement therapy (RRT), ferritin, intravenous iron, as well as others. Using a logistic regression multivariate analysis, the study revealed that female gender (RR 2.17; p=0.01), increasing duration since first dialysis (RR 1.06 per year; p=0.03), and increased body weight (RR 1.02 p= 0.02) were independent risk factors for RLS. Iron status and anemia were not found to be statistically associated with risk for RLS.

Clardy, Earley, Allen, et al., (2006): The authors evaluated CSF ferritin levels and brain iron status in patients with RLS to determine if brain iron was insufficient. Patients enrolled had to have “nightly symptoms before treatment for at least 6 mos, show a positive clinical response to dopaminergic agents, and have PLMS > 20/hour when off of medications. Patients developing RLS in relationship to other specific causes like anemia, iron deficiency, renal dialysis, peripheral neuropathy, neurodegenerative disorder, or other obvious medical problems or medications were excluded…” CSF was collected from 25 subjects with RLS (12 early-onset and 13 late-onset) and 14 control subjects who did not have RLS. H and L ferritin subunits as well as total protein from the CSF were measured in all subjects. [Ferritin molecules are composed of 2 subunit types: H & L. H chains are important in ferrous iron oxidation, and L chains reflect long term iron storage.] The results of the study revealed that both H and L subunits were significantly lower in early but not late onset RLS subjects compared to non-RLS subject, and total volume of CSF protein was not different between the two groups despite the reduction in ferritin subunits.

4. MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

We did not find evidence-based guidelines on the use of ferritin levels for diagnosing or monitoring therapy related to restless leg syndrome.

6. Professional Society Position Statements

The American Academy of Sleep Medicine endorses the addition of restless leg syndrome to the ICD-9-CM Codes Covered by Medicare Program list for the Serum Iron NCD. A number of articles including the “Standards of Practice Committee of the American Academy of Sleep Medicine” were included with its statement.

7. Expert Opinion

We have not received any expert opinions on the use of serum iron studies for therapy related to RLS.

8. Public Comments

Initial public comments

We received 5 public comments during the initial public comment period. One was from a professional society: the American Academy of Sleep Medicine. Another was from a patient advocacy group: The Restless Legs Syndrome Foundation. Both endorsed adding RLS to the ICD-9-CM code list of covered indications for the Serum Iron Studies NCD. The remaining commenters were a patient and two administrators; all supported the inclusion of RLS on the covered indication list. One commenter felt CMS held RLS “…to a higher standard than other diagnoses that are currently on many of the National Coverage Decisions.” Only the American Academy of Sleep Medicine included published scientific evidence, which was included in the CMS analysis.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." §1862(a) (1) (A). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment question:

Is the quality of evidence adequate to conclude that the results of serum testing for iron, ferritin, iron binding capacity and/or transferrin, when used by the treating physician to guide management of the patient's medical problem, improve health outcomes in persons with restless leg syndrome?

- Is there adequate evidence that accepted diagnostic criteria require serum iron testing results for the diagnosis of RLS?
- Is there adequate evidence that iron supplementation, which would then be accompanied by serum iron studies testing to monitor the treatment, is necessary to treat RLS?

Use of Iron Studies as a Screening or Diagnostic Tool for RLS:

Because Medicare coverage of screening for asymptomatic persons is generally excluded by statute unless expressly provided by Congress, we will focus on the diagnostic use of serum iron testing for RLS. Some authors report an inverse relationship between serum ferritin and symptoms related to RLS. Others report an association with CSF ferritin/transferrin levels and RLS. Some note no association between serum ferritin/iron studies and RLS. And finally, when studying RLS and CSF ferritin/transferrin and serum levels concomitantly, some studies showed an association between RLS and the former, but failed to show a relationship with RLS and the latter. In some studies patients with ferritin levels around 50 mcg/l were the well controls, in other studies comparable values were associated with sever RLS symptoms. Any relationship between ferritin/transferrin/iron studies and RLS is apparently very complex. Testing for CSF ferritin is not the same as measuring serum ferritin, and the Serum Iron Studies NCD does not speak to measurement of CSF ferritin. Thus CSF ferritin is outside of the scope of this NCD.

In assessing serum ferritin/transferrin/iron studies as a potential test used in the detection of RLS, a significant limitation is the lack of measures of accuracy. Measures of accuracy (e.g., sensitivity, specificity, positive predictive value-PPV, and negative predictive value-NPV) must be known if we are to determine the ability of a test to correctly identify diseased and well persons in a given population. Receiver operator characteristic (ROC) curves and likelihood ratios can also be used. None of the studies reviewed provided any information on these measures of accuracy. Most of the studies included in this analysis were cross-sectional studies, which are observational in nature. One difficulty of a cross-sectional design is its inability to establish causal relationship (i.e., it does not establish sequence of events). Though a number of these cross-sectional studies were able to show a moderate to good correlation between ferritin levels and RLS, association does not mean causation. Two studies included in this analysis were prospective, and were more useful to determine if knowing serum iron study levels improved the prognosis or management of patients with RLS.

Confounding could also be a limitation of these observational studies. As demonstrated in a number of studies, CSF ferritin seemed to be more associated with RLS symptoms than serum ferritin levels. Most studies only evaluated serum ferritin/transferrin/iron studies. The use of multivariate analysis or other research designs (e.g., specification, matching, stratification) could have controlled for confounding and shown the true relationship between serum ferritin/transferrin, iron studies and RLS.

The reported age-associated association of anemia and RLS does not necessarily indicate a causal relationship. Advancing age is associated with other factors, such as mal- and under-nutrition, chronic disease, and malignancy, which also cause anemia. We are not confident that coincidental covariability has been adequately excluded by the available evidence. In addition, ferritin is an acute phase reactant, and the significance of this as a confounder was not addressed in most of the reports. In some reports serum iron was normal in the face of low ferritin. Thus it becomes difficult to separate the extent to which ferritin levels reflected iron status versus inflammation or alterations in protein status. Bone marrow sampling for stainable iron was not reported.

A limitation of many of the reviewed studies is small sample size. Cross-sectional sampling is a technique which could have been used to improve validity and interpretable results. This was not used.

Effect of iron supplementation on RLS symptoms:
Using serial iron study testing in a prospective manner, several authors have claimed that iron supplementation helps to relieve RLS symptoms, at least in the short term, generally 2 weeks. However, the reports are limited by lack of blinding, lack of controls, and very small sample sizes. Some trials studied ESRD patient on dialysis, which makes it difficult to generalize the results to the Medicare population at large. A randomized placebo-controlled trial showed that iron supplementation is not helpful in this condition. Another randomized placebo-controlled trial of carbamazepine demonstrated a large positive placebo effect in RLS. The frequent exclusion of patients who had recently taken iron supplementation further limits the conclusions that can be confidently asserted. We believe that there is insufficient evidence to determine that iron supplementation is generally beneficial in the treatment of persons with RLS. Though this NCD is not specifically about the use of iron supplementation to treat RLS, consistent strong evidence supporting such treatment could have been informative about a possible role for the monitoring of serum iron studies in RLS patients.

Patients with RLS who have other indications for serum iron studies testing:
Many of the reports described patients with RLS who had currently covered indications for testing, including anemia, chronic renal disease with or without dialysis, and vitamin B_{12} deficiency. We cannot determine from the evidence reviewed that an additional benefit would be realized if RLS itself were presumed to indicate medical necessity.

Analysis of Individual Articles:

Nordlander, (1953): This is an uncontrolled, apparently unblinded and non-randomized case series. The author noted the same response to iron therapy whether or not the patient was iron deficient. Other laboratory measures of iron status were incompletely reported, but he noted that 2 of his successfully treated patients had normal iron-binding capacity. This suggests that the results of serum iron studies are not relevant to the treatment of RLS. He states, “In the light of these experiences it is difficult to explain the favorable effect of intravenous iron treatment on the theory that restless legs might…be a sign of iron deficiency.” Later he notes, “…there are great spontaneous variations in the symptoms.”

Ekbom, (1960): This is a clinical review with reports of personal practice experience without description of systematic criteria for subject selection, blinding, controls, or assessment. Neither individual patient results nor summary data were provided.

Telstad, Sørensen, Larsen et al., (1984): Explicit diagnostic criteria for RLS were not described. Though the authors did provide a general description of the characteristic symptoms that is compatible with more stringent criteria, this remains a weakness in comparing their conclusions to more modern studies. This large randomized placebo-controlled trial of carbamazepine demonstrated a significant therapeutic placebo effect in RLS treatment. This is an important finding for the interpretation of the many small, non-randomized, uncontrolled trials of iron supplementation in RLS.

O'Keeffe, Noel, Lavan, (1993): In this study the diagnostic criteria used to make a diagnosis of RLS were not consistent with criteria currently used (based on IRLSSG). Also, the ferritin level used in this study to mark iron deficiency (<18 µg/l) is inconsistent with ferritin levels most commonly used to note deficiency (<45- 50 mcg/l.) This study also does not mention how severity of symptoms was determined. Three iron deficient patients were treated in this open-label study with ferrous sulfate and completed the study. A fourth patient died before completion. The one patient with RLS and vitamin B_{12} deficiency noted complete resolution of their symptoms after being treated with vitamin $B_{12,}$ suggesting an alternate disease mechanism. The lack of blinding or controls and the very small sample size are significant limitations, and we do not believe that confident conclusions can be drawn about the role of iron supplementation in RLS can be made from the reported results.

O'Keeffe, Gavin, Lavan, (1994): This is a small, unblinded, uncontrolled study. Some subjects chose whether or not to take iron supplementation. The criteria used to diagnose RLS were not described.

Aul, Davis, Rodnitzky, (1998): This is a brief report in the Clinical/Scientific Notes section of the journal. Thus few details are available for review. It is a retrospective review of records and the previously obtained laboratory values were not consistently available in all patients. For example, only 48/113 (42%) of patients had serum iron studies. This lack of systematic assessment makes it problematic to draw confident conclusions from the reported data. The authors do not compare the findings in RLS patients to non-RLS patients. We cannot, from the available data, exclude the likelihood that reduced ferritin is a non-specific finding.

Collado-Seidel, Kohnen, Samtleben, et al., (1998): No significant relationship was found between serum iron, ferritin, or transferrin. This study only enrolled dialysis patients so it is difficult to generalize the results to the general Medicare population.

Sun, Chen, Ho et al., (1998):

This retrospective study analyzed data on subjects who had had a ferritin level obtained at the time they had had a PSG. This introduces a source of exclusion bias, as apparently not all patients with RLS had a ferritin level. The exclusion of almost three-quarters of the presenting RLS patients creates doubts about the generalizability of the conclusions. The exclusion of patients who had been taking iron supplementation creates uncertainty about whether a ferritin level would be useful in monitoring a patient on iron therapy for RLS or taking iron therapy for some other indication that may coexist with RLS.

Chesson, Wise, Davilla, et al., (1999): Based on the AASM classification of evidence as adapted from Sackett, this recommendation was given an evidence level of III to V, based on non-randomized controlled or concurrent cohort studies, non-randomized historical cohort studies, and case series. It was also given a recommendation grade of C (which is the lowest recommendation grade), and was labeled an option. As noted in this practice parameter, an option “is a patient care strategy which reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.”

Allen, Earley, (2000):
Sample sizes of 14 and 12 respectively, were small in both the early- and late-onset groups. In the late-onset group, there were only 2 subjects with JHRLSS scores of one, indicating mild symptoms. One of these subjects had a ferritin level between 10 and 20 mcg/l while the other had a ferritin level between 100 and 110 mcg/l. (Individual numerical data are not provided, requiring estimation from the provided figures.) This is a retrospective analysis and not a therapeutic trial of iron supplementation.

Davis, Rajput, Rajput, Aul, Eichhorn, (2000): This was a randomized, double-blind placebo-controlled study to see if RLS symptoms improved with supplemental iron. The results of the study revealed that there was no significant difference between iron and placebo groups regarding improvement in quality of sleep, proportion of nights with RLS symptoms, and level of RLS effect on their life, and more than half of patients in the iron supplement group had adverse effects related to the ferrous sulfate. Though the visual analog scale (VAS) is validated for measuring pain, very few studies have used this instrument for measuring severity of illness in the RLS population. The drop out rate was high, particularly in the group treated with iron. This suggests that iron therapy, even if indicated, is likely to be a less than ideal therapeutic strategy in a community setting without the support for patient compliance that is available in the context of a clinical trial.

Earley, Connor, Beard, et al., (2000): This study is limited by small sample size (n=16), and the inclusion criteria included a positive clinical response to levodopa as well as clinical severity. The diagnosis of RLS is already clear-cut in these patients by the time they have met the entry criteria, thus serum iron studies would seem to have no incremental diagnostic value. The results support the model of RLS resulting from abnormalities of iron metabolism in the brain. However, this report does not address the effect of serum iron studies on health outcomes of persons who have RLS.

Allen, Barker, Wehrl, et al., (2001): This is a small preliminary study with only 5 RLS patients. As the authors noted, “All patients with RLS also had been treated with dopaminergic medications, which could possibly have affected brain iron concentrations. Further studies with larger sample sizes and, ideally, with patients off RLS-related medications are needed to confirm these results.” It lends support to the model of RLS resulting from abnormalities of iron metabolism in the brain. However, it does not address the effect of serum iron studies on health outcomes of persons who have RLS.

Allen, Earley, (2001): As a clinical review this report does not carry the evidentiary weight of a systematic review, original research, or a meta-analysis. Though it was an informative summary of the theorized pathophysiology of RLS and proposed role of iron, it does not establish the usefulness of serum iron studies in the diagnosis or treatment of RLS.

Berger, von Eckardstein, Trenkwalder, Rothdach, et al., (2002): This large cross-sectional study failed to find an association of RLS with soluble transferrin receptor or ferritin, and the authors concluded that the changes iron metabolism were more complex than iron or ferritin deficiency. Though not quite reaching statistical significance, the results display a bimodal response in that RLS was most strongly associated with the 4th and 1st quintiles of iron and transferrin saturation, while the 2nd and 3rd quintiles have lower values. Thus it does not appear that serum iron studies testing would be generally helpful in making a diagnosis of RLS.

Ondo, Dat Vuong, Jankovic, (2002): Since ferritin testing was performed non-systematically, i.e., at variable periods (3 – 10 months) after the survey and on only a fraction of the total subjects, we cannot be confident that a conclusion can be drawn or that the results can be generalized to other patients with RLS symptoms. All the patients had Parkinson's disease, which limits the generalizability of the conclusions to other patients with RLS. These limitations and others were acknowledged by the authors.

Connor, Boyer, Menzies, et al., (2003): Though this study suffers from inadequate sample size, it lends support to the model of RLS resulting from abnormalities of iron metabolism in the brain. However, it does not address the effect of serum iron studies on health outcomes of persons who have RLS.

Garcia-Borreguero, Odin, Serrano, (2003): This is a clinical review of possible underlying pathophysiologic mechanisms rather than a systematic review of diagnostic or therapeutic outcomes. The authors note that large clinical trials are needed.

Silber, Richardson, (2003): This study reported on a very select subset of patients with RLS who met inclusion criteria that included low ferritin (8/245 patients) and significant blood donation. We cannot generalize these findings to the RLS population at large.

Connor, Wang, Patton, et al., (2004: Though this study has only 8 subjects, it does tend to support that neurodegeneration is associated with RLS. However, it does not address the effect of serum iron studies on health outcomes of persons who have RLS.

Earley, Heckler, Allen, (2004): This study was uncontrolled and unblinded, and the primary outcome was subjective, i.e. the patient's self-reported need for medication. The ultimate sample size was quite small (10 subjects) and the absolute numbers of patients classified as Non-Responders and Responders were only 4 and 6 respectively. The classification was performed at the two week assessment, and it is not clear why this particular time point was chosen. If the classification had occurred instead at 3 months, the number of Responders and Non-Responders would have been equal. It appears that all subjects eventually reached the primary endpoint after a mean 11.3 months. It is not apparent that additional iron supplementation would prolong this period. One Responder had a GRS score lower than the mean of the Non-Responder group, and a different Responder had a PLMS/h decrease lower than the mean for the Non-Responder group. And another Responder had a decrease with RLS score that was lower than a Non-Responder. Thus 3/6 Responders had scores that were in part compatible with Non-Responders. Levels of iron concentration in the brain also were noted to increase, though there was no statistical difference between Responder and non-responders, and levels of ferritin fell faster than predicted. The ferritin levels were reported to drop rapidly after treatment, but the Non-Responders apparently had a slower rate of decline than the Responders, though the difference was not reported as statistically significant. If ongoing iron loss predisposes patients to RLS symptoms, it is unclear why the RLS symptoms would be worse in the patients who had a lower rate of iron loss. This study also excluded patients with RLS with anemia, so it is difficult to generalize these findings to Medicare RLS patients with anemia. Considering the small number of subjects, the lack of blinding and control, and the subjective nature of the primary endpoint, we cannot confidently conclude from this report that iron supplementation is generally beneficial for patients with RLS.

Mizuno, Mihara, Miyaoka, et al., (2004): This study is limited by small sample size (10 RLS and 10 controls). The results support the model of RLS resulting from abnormalities of iron metabolism in the brain. However, this report does not address the effect of serum iron studies on health outcomes of persons who have RLS.

Silber, Ehrenberg , Allen, Buchfuhrer et al., (2004): This is a clinical review. Though the author does note the importance of evidence-based medicine reviews in the treatment of RLS, there is no evidence-based support provided demonstrating the effectiveness of iron in patients with RLS. The patients for whom ferritin testing is encouraged, i.e., persons with conditions that predispose to blood loss, would be covered for serum iron testing on the basis of those conditions by the current NCD.

Sloand, Shelly, Feigin, et al., (2004): One of the limitations of this study is its small sample size (n=25). Another limitation of the study is the questionnaire that was used to determine severity of illness. The questionnaire used in this study contains 3 questions (each offering 4 to 5 graduated choices), while the IRLSSG (validated instrument) contains 10 questions. Using a different instrument to measure severity of illness for RLS subjects is a threat to internal validity, thus making this study not comparable to others using the validated instrument. Since participants in this study suffered with ESRD and were on dialysis, findings from this study are difficult to generalize to the non-ESRD, non-dialysis Medicare population.

Earley, Connor, Beard, Clardy, Allen, (2005): One limitation of this study is the small sample size (n=30). Though the study noted a moderate correlation between age of symptoms and CSF ferritin levels (r=0.64), there was no attempt made to determine a correlation between age of symptoms and serum ferritin levels, nor was there an attempt to determine if a correlation existed between CSF and serum ferritin levels. In this setting, if a strong correlation existed between CSF and serum ferritin, this could be used to bolster the use of serum ferritin as a marker to distinguish between early- and late-onset RLS. But this information alone does not help us in determining causation of disease (e.g., association/correlation does not mean causation). Obtaining CSF ferritin levels for diagnostic purposes is not a very practical procedure due to the inherent risk, especially since the diagnosis of RLS is based solely on clinical criteria.

Earley, Heckler, Allen, (2005): Earley and associates later performed a follow up study of the same six subjects who noted improved symptoms after receiving iron infusion in the 2004 study. Of the 5 subjects eligible for follow-up, only 3 completed the 2-year study. Though the study revealed that the slower the rate of ferritin decline, the more prolonged the symptom improvement, it was hampered due to the low sample size (n=5) as well as the lack of blinding and controls during the treatment phase. The same limitations of the 2004 Earley et al. study are limitations of this follow-up study.

Hogl, Kiechl, Willeit et al., (2005): This cross sectional study failed to find an association of RLS with free serum iron, transferrin, or ferritin. The test for which there was a statistically significant difference between persons with RLS and normal persons, soluble transferrin factor, is not a component of the Serum Iron Studies NCD and is thus not pertinent to this NCD.

O'Keeffe, (2005): The author studied secondary causes of RLS and was able to demonstrate that iron deficiency anemia increased in frequency as patients got older. A weakness of this study is the reliance on self-reporting of onset of symptoms by participants. Also as noted by the study, "…findings reported from a hospital-based service with a well-established interest in RLS may not be fully applicable to RLS patient sufferers in the general population."

O'Keeffe, (2005): Individual case reports, though they may be informative for hypothesis generation, do not provide sufficient generalizable information to carry more than minimal evidentiary weight.

Siddiqui, Kavanagh, Traynor et al., (2005): This study had a larger number of RLS patients than most of the others we reviewed. No association with iron status was noted. As all the subjects were undergoing hemodialysis, the generalizability of the conclusions to the Medicare population at large is uncertain.

Clardy, Earley, Allen, et al., (2006): This study is limited by small sample size. It lends support to the model of RLS resulting from abnormalities of iron metabolism in the brain. However, it does not address the effect of serum iron studies on health outcomes of persons who have RLS.

Summary

The evidence reviewed in this decision memorandum suggests that brain iron metabolism likely has a role, albeit incompletely elucidated, in the pathophysiology of RLS. The evidence does not establish a clear and consistent relationship between the diagnosis of RLS and serum testing for iron and related substances, nor does it confirm the value of RLS treatment with supplemental iron. Thus we do not find that a presumption of coverage is warranted for the use of serum iron studies in beneficiaries with RLS.

IX. Conclusion

CMS is seeking public comment on our proposed determination that there is insufficient evidence to add restless legs syndrome as a covered indication in the narrative of the Serum Iron Studies National Coverage Determination (NCD) at Section 190.18 of the NCD Manual. Local Medicare contractors may continue to provide coverage on a case by case basis based on additional documentation submitted by the provider with the claim.

We propose to issue a National Coverage Determination (NCD) that does not change the current Serum Iron Studies NCD. That is, restless legs syndrome would remain on the ICD-9-CM Codes that Do Not Support Medical Necessity list, and providers seeking coverage for the clinical laboratory diagnostic test would continue to submit additional documentation to support a determination of medical necessity.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

Appendices[PDF, 114KB]

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